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Wehrmann, T., et al. Endoscopic botulinum toxin injectioninto the minor papilla for treatment for treatment for idiopathic recurrent pancreatitis in patients with pancreas
divisum, **Gastrointestinal Endoscpoy, vol. 50, No. 4, 1999 pp. 545-548**, XP-000971257.

Okolo, P.I., et al., Immediate reduction of pancreatic so pressure after endoscopic injectionof botulinum toxin (BoTox): implications of prevention of ERCP-induced
pancreatitis, **Gastroenterology, vol. 114, No. 4, Part 2, Apr. 1998, p. A535**, XP-000971724.

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NEW METHODS & MATERIALS

Endoscopic botulinum toxin injection into the minor papilla for treatment of idiopathic recurrent pancreatitis in patients with pancreas divisum

Till Wehrmann, MD, Thomas Schmitt, MD, Hans Seifert, MD

Background: In some patients with pancreas divisum, obstruction to the flow of pancreatic juice into the duodenum is the presumptive cause of acute recurrent pancreatitis. However, identification of those patients who may benefit from minor papilla sphincterotomy or stent placement is difficult.

Methods: Five patients with acute recurrent pancreatitis and pancreas divisum were therefore treated by endoscopic injection of 50 units of botulinum toxin into the minor papilla in an outpatient setting.

Results: Botulinum toxin injection was successfully performed on six occasions in 5 patients and no adverse effects were noted. Two patients relapsed after 9 and 10 months, respectively, but had definite relief of symptoms after needle-knife sphincterotomy. One patient relapsed 7 months after botulinum toxin injection but became symptom free again after a second botulinum toxin injection. Another patient is still in clinical remission 4 months after botulinum toxin administration, and 1 patient did not respond to either botulinum toxin administration or to sphincterotomy and stent placement.

Conclusions: Endoscopic injection of botulinum toxin into the minor papilla in patients with pancreas divisum and acute recurrent pancreatitis is a safe procedure that is easy to perform and provides short-term relief in some patients. Response to botulinum toxin injection may predict whether patients with pancreas divisum and acute recurrent pancreatitis will benefit from other forms of endoscopic therapy.

Pancreas divisum is a common congenital anomaly with an estimated prevalence of 5% to 7% in the general population.[1-5] Because a greater volume of the pancreatic secretion drains through the small minor papilla in this situation, it has been speculated that this presumptive obstruction to outflow may cause recurrent attacks of pancreatitis in a subset of patients.[1-5] Although the putative relationship between acute recurrent pancreatitis (ARP) and pancreas divisum continues to be controversial, balloon dilation, endoscopic sphincterotomy, and accessory duct stent placement have been performed in this setting.[6-12] However, the response rates have varied between 20% and 90% and endoscopic therapy has risks.[6-12] Therefore, data to guide selection of patients who may benefit from ductal decompression would be useful. Because local injection of botulinum toxin (BTX) has been proven to transiently relax the smooth muscle of GI sphincters,[13-19] we undertook a study of endoscopic BTX injection into the minor papilla.

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PATIENTS AND METHODS

Patients

From October 1995 to May 1998 we offered endoscopic BTX injection into the minor papilla to all patients who had experienced two or more episodes of abdominal pain with associated serum amylase elevations twice the range of normal during the previous 6 months (at least one pancreatitis episode every 3 months) and in whom pancreas divisum was verified by pancreatography. Excluded were patients in whom other causes of ARP (alcohol, gallstones, trauma, medication related, metabolic disorders, sphincter of Oddi dysfunction of the major papilla, or family history) could be identified. Chronic pancreatitis was ruled out in each case by normal findings by abdominal US, CT, pancreatography (no duct dilatation or other abnormalities except the presence of separated pancreatic anlage) and normal stool weight, fat and elastase concentrations (3-day analysis). During the study period 5 patients agreed to participate (another qualified patient declined). None of the patients had prior abdominal surgery except appendectomy. Endoscopic retrograde cholangiography with additional analysis for bile crystals was normal in all patients, and biliary and pancreatic sphincter of Oddi dysfunction of the major papilla was excluded by manometry in 3 cases (Table 1). Sphincter of Oddi manometry of the minor papilla was performed in 4 patients (in the remaining patient, cannulation of the minor papilla could not be achieved with the manometry probe) and revealed sphincter hypertension in all (extrapolating from data pertaining to the major papilla, an abnormal pressure was considered present if the pressure exceeded 40 mm Hg, Table 1).[10,11] None of the episodes of pancreatitis in the study patients was related to a medical procedure.

All patients gave written informed consent before BTX treatment, and the study protocol was approved by the ethics committee of our university.

Endoscopic procedure

After an overnight fast the duodenum was intubated with a side-viewing endoscope (TJF 130 or 140; Olympus Optical, Hamburg, Germany) under satisfactory sedation with intravenous propofol (Disoprivan; Zeneca, Plankstadt, Germany) and the minor papilla was visualized. Then, 50 units of BTX (Botox; Pharma Merz, Frankfurt am Main,

Figure 1. Duodenoscopic appearance of the minor papilla in patient No. 3 during endoscopic injection of 50 units BTX (injection volume 0.5 mL) into the papillary roof through a standard sclerotherapy needle.

Germany), reconstituted in 0.5 mL physiological saline, was injected into the papillary roof as a single deposit through a standard sclerotherapy needle (0.5 mm diameter, 5 mm needle length) (Fig. 1). The minor papilla was not cannulated and the procedure was performed on an outpatient basis with clinical monitoring in the endoscopy unit for 4 hours after the procedure. Patients remained fasting overnight and were routinely interviewed for side effects during the evening of the procedure day and the next morning via telephone. All patients were evaluated clinically 4 to 6 weeks after treatment and were followed at bimonthly intervals thereafter. A clinical response was defined as a symptom-free period of more than 3 months' duration after endoscopic BTX injection.

RESULTS

BTX injection into the minor papilla was technically successful in all patients and no side effects (e.g., bleeding or postprocedure pancreatitis) were noted. Endoscopically, slight edema of the minor papilla was observed immediately after BTX injection on one of six occasions. The average duration of the procedure was 8 minutes (range 5 to 10 minutes, time span from insertion of the endoscope to withdrawal).

The first 2 patients remained free of complaints for 9 and 10 months, respectively (Table 1). Thereafter, both patients had a relapse of acute pancreatitis. Both underwent minor papilla needle-knife sphincterotomy over a previously placed 7F straight stent (which was removed 3 days later) and had an uneventful long-term clinical course thereafter. Another patient remained symptom free for 7 months after BTX injection. After a recurrent episode of acute pancreatitis he underwent a second BTX injection into the minor papilla (because he refused sphincterotomy) and again became free of complaints. One patient treated by BTX injection 4 months ago remains free of symptoms.

Repeated manometry of the minor papilla indicated recurrence of sphincter hypertension in all 3 patients with relapse after BTX treatment (Table 1). Another patient had a documented episode of acute pancreatitis 1 month after BTX injection (BTX nonresponder). Minor papilla sphincterotomy and stent placement (7F straight stent) were perfomed 2 weeks later but the patient developed another episode of acute pancreatitis 2 months thereafter.

DISCUSSION

The precise relationship between pancreas divisum and ARP is largely unknown. It has been suggested that resistance to the flow of secretions through the relatively small minor papilla causes ductal hypertension and recurrent attacks of pancreatitis.[1-5] Therefore, current endoscopic therapy is directed toward relieving the presumptive outflow obstruction by sphincterotomy of the minor papilla or long-term accessory duct stent placement; the results of such therapy in selected cases are reasonable.[6-12] However, minor papilla sphincterotomy has been associated with postprocedural pancreatitis in nearly 20% of cases, and stent migration or ductal irregularities resulting from long-term stent placement have been observed in up to half of the cases.[6-12] Therefore, identification of those patients who may benefit from endoscopic therapy is a major consideration. Endoscopic manometry of the minor papilla is hampered by the lack of true normal values,[11] and the diagnostic relevance of the occasional US demonstration of pancreatic duct dilatation after stimulation by intravenous injection of secretin remains to be proved.[20]

Endoscopically guided injection of BTX into the minor papilla may in theory offer some advantages. By blockade of acetylcholine release from presynaptic cholinergic nerve endings, locally administered BTX can significantly lower the basal tone of GI smooth muscle sphincters, an effect that is generally fully reversible after 5 to 16 months.[13-19] Furthermore, it has been proved that local BTX injection into the major papilla is a technically easy and relatively safe procedure.[15,16] Based on our results in patients with biliary sphincter of Oddi dysfunction that indicate that BTX injection into the sphincter of Oddi can predict whether patients will benefit long-term from endoscopic sphincterotomy,[16] we investigated the clinical effects of BTX

Table 1. Demographic and manometric data f r 5 patients with ARP and pancreas divisum and their clinical course after endosc pic injection of BTX into the min r papilla

Parameter	Patient No. 1	Patient No. 2	Patient No. 3	Patient No. 4	Patient No. 5
Age (yr)	24	39	44	50	64
Gender	Male	Female	Male	Female	Female
Attacks of ARP (no. during 6 mo before study entry)	3	4	3	2	6
(B) BSOP (mm Hg)	28	17	22	Not done	Not done
(P) BSOP (mm Hg)	24	18	26	Not done	Not done
MPSBP (mm Hg)	65	44	51	Not done	49
Symptom free after BTX-injection (mo)	9	10	7	1	4
MPBSP at relapse (mm Hg)	53	45	41	Not done	No relapse
Treatment after relapse	MP-NKS	MP-NKS	2nd BTX injection	MP-NKS + stenting	No relapse
Final outcome (mo of follow-up after relapse)	Remission (22)	Remission (18)	Remission (9)	Relapse of ARP	No relapse

(B) BSOP, Biliary sphincter of Oddi baseline pressure; *(P) BSOP*, pancreatic sphincter of Oddi baseline pressure; *MPSBP*, minor papilla sphincter baseline pressure; *MP-NKS*, minor papilla needle-knife sphincterotomy.

injection into the minor papilla of patients with pancreas divisum and ARP.

Analogous to the situation at the major papilla, BTX injection into the minor papilla was quick and easy to perform (because ductal cannulation is unnecessary) on all six occasions (including one retreatment) and no side effects were observed. However, in our series of patients undergoing BTX treatment for biliary sphincter of Oddi dysfunction, mild pancreatitis occurred in 1 of 22 cases.[16] Short-term response (3 to 10 months) to BTX treatment was documented in 4 of 5 patients with ARP and pancreas divisum. Those patients who had relapses of pancreatitis after the initial BTX treatment became again free of complaints after needle-knife sphincterotomy or a second BTX injection. The patient who did not respond to BTX treatment also had no benefit from endoscopic therapy (sphincterotomy and stent placement).

In summary, our initial experience in 5 patients demonstrates the technical feasibility and safety of BTX injection into the minor papilla. The results may indicate that a response to BTX injection identifies patients with pancreas divisum in whom outflow obstruction at the minor papilla causes ARP. However, this was not a randomized trial and only patients with frequent relapsing pancreatitis (mean 3.6 ± 1.5 episodes during the 6 months before study entry) were enrolled, which may result in a significant selection bias. Therefore, a randomized trial involving a larger cohort of patients is warranted.

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Preoperative assessment of extrahepatic bile duct carcinoma using three-dimensional intraductal US

Kiichi Tamada, MD, Takeshi Tomiyama, MD, Akira Ohashi, MD, Shinichi Wada, MD, Yukihiro Satoh, MD, Takamitsu Miyata MD, Kenichi Ido, MD, Kentaro Sugano, MD

Background: **We investigated the utility of a new imaging modality, three-dimensional intraductal ultrasonography (US), for staging bile duct cancer.**
Methods: **In eight patients with extrahepatic bile duct carcinoma, two- and three-dimensional intraductal US was used to assess tumor invasion of the right hepatic artery, portal vein, and pancreatic parenchyma before resection. The findings were correlated with histologic information from the resected specimen.**
Results: **Three-dimensional intraductal US enabled accurate assessment of tumor invasion of the right hepatic artery in 88% of cases, the portal vein in 100%, and pancreatic parenchyma in 100%. Two-dimensional intraductal US enabled accurate assessment of invasion of these structures in 88%, 88%, and 88% of cases.**
Conclusions: **Three-dimensional intraductal US is useful in assessing tumor stage in bile duct carcinoma.**

Intraductal ultrasonography (IDUS) with a high-frequency probe has been used to obtain high-quality cross-sectional images of the bile ducts in real time.[1-16] Our research group[1-10] and others[11-16] have previously reported the utility and limitations of two-dimensional IDUS (2D-IDUS) in staging bile duct cancer. Kanemaki et al.[15,16] reported the utility of three-dimensional IDUS (3D-IDUS) in cases of pancreatobiliary disease. They preoperatively evaluated tumor invasion of the portal vein in four patients with bile duct cancer, one with gallbladder cancer, and one with pancreatic cancer.[15] We investigated the reliability of 3D-IDUS in assessing tumor invasion of the hepatic artery, portal vein, and pancreatic parenchyma in patients with bile duct carcinoma before resection and compared sonographic assessments with histologic findings in the resected specimens.

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PATIENTS AND METHODS

Patients

Eight consecutive patients (6 men, 2 women) with extrahepatic bile duct carcinoma underwent tumor staging with 3D-IDUS before surgical resection between December 1997 and September 1998. Mean patient age was 66.1 years (range 56 to 84 years). Surgical staging identified one lesion as T1 and seven as T3 (Table 1). Written informed consent was obtained from all patients before percutaneous transhepatic biliary drainage, endoscopic retrograde cholangiography, and IDUS.

Equipment

The 3D-IDUS system (Fujinon Co., Ltd., Saitama, Japan) consists of small-diameter US probes (diameter 2.0 mm; 12 and 20 MHz), a probe translator (SP-501), a US unit (SP-701), and a 3D unit (TP-101). The probes and the US unit for 3D-IDUS were the same as for conventional 2D-IDUS. Only the probe translator and 3D-unit were designed specifically for 3D-IDUS. Probes with a 20 MHz frequency provided axial resolution of 0.1 mm and maximum penetration of approximately 20 mm. Probes with a 12 MHz frequency provided axial resolution of 0.3 mm and maximum penetration of approximately 30 mm.

The 3D-IDUS system displays radial and linear scans in real time. Radial images were made with a 360-degree scan perpendicular to the tip of the probe. The linear dimension was added by integrating 40 serial radial scan images obtained at uniform intervals during one scanning pass and stored digitally. To obtain the linear images, the US probe was moved lengthwise for 20 mm over about 3 seconds by means of the translator. Although the translator was moved manually, the linear images were constructed automatically and uniformly, even when the bile duct was not scanned at uniform speed. Three-dimensional images were produced automatically as stereographic views within a few seconds after the procedure by means of selection of a region of interest from the radial and linear images.

Technique

The probe was inserted into the bile duct through a

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TI Peripherally induced oromandibular dystonia.
AU Sankhla, Charulata; Lai, Eugene C.; Jankovic, Joseph [Reprint author]
CS Movement Disord. Cin., Dep. Neurol., Baylor Coll. Med., 6550 Fannin, Suite 1801, Houston, TX 77030-3498, USA
SO Journal of Neurology Neurosurgery and Psychiatry, (Nov., 1998) Vol. 65, No. 5, pp. 722-728. print.

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Peripherally induced oromandibular dystonia

Charulata Sankhla, Eugene C Lai, Joseph Jankovic

Abstract

Objectives—Oromandibular dystonia (OMD) is a focal dystonia manifested by involuntary muscle contractions producing repetitive, patterned mouth, jaw, and tongue movements. Dystonia is usually idiopathic (primary), but in some cases it follows peripheral injury. Peripherally induced cervical and limb dystonia is well recognised, and the aim of this study was to characterise peripherally induced OMD.

Methods—The following inclusion criteria were used for peripherally induced OMD: (1) the onset of the dystonia was within a few days or months (up to 1 year) after the injury; (2) the trauma was well documented by the patient's history or a review of their medical and dental records; and (3) the onset of dystonia was anatomically related to the site of injury (facial and oral).

Results—Twenty seven patients were identified in the database with OMD, temporally and anatomically related to prior injury or surgery. No additional precipitant other than trauma could be detected. None of the patients had any litigation pending. The mean age at onset was 50.11 (SD 14.15) (range 23–74) years and there was a 2:1 female preponderance. Mean latency between the initial trauma and the onset of OMD was 65 days (range 1 day-1 year). Ten (37%) patients had some evidence of predisposing factors such as family history of movement disorders, prior exposure to neuroleptic drugs, and associated dystonia affecting other regions or essential tremor. When compared with 21 patients with primary OMD, there was no difference for age at onset, female preponderance, and phenomenology. The frequency of dystonic writer's cramp, spasmodic dysphonia, bruxism, essential tremor, and family history of movement disorder, however, was lower in the post-traumatic group ($p<0.05$). In both groups the response to botulinum toxin treatment was superior to medical therapy ($p<0.005$). Surgical intervention for temporomandibular disorders was more frequent in the post-traumatic group and was associated with worsening of dystonia.

Conclusion—The study indicates that oromandibular-facial trauma, including dental procedures, may precipitate the onset of OMD, especially in predisposed people. Prompt recognition and treatment may prevent further complications.

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Keywords: oromandibular dystonia; peripheral trauma; bruxism; dental surgery; botulinum toxin

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Peripheral trauma has been implicated as a cause or a predisposing factor in various neurological disorders[1–3] and in various movement disorders such as Parkinson's disease and tremors,[4] dystonia,[5–13] painful legs and moving toes,[14] and myoclonus[15] The relation between trauma and the subsequent development of a movement disorder, particularly dystonia and tremor, has been documented in many reports.[4 15]

Oromandibular dystonia (OMD) is a focal dystonia involving the mouth, jaw, and tongue causing involuntary mouth closure or opening, deviation of the jaw, facial grimacing, or tongue movements. It often interferes with chewing, swallowing, and speaking. In addition, its appearance is often socially embarrassing and cosmetically disfiguring. When associated with dystonia of the upper face, such as blepharospasm, the term "cranial dystonia" is used[16] The aetiology of OMD is usually unknown, but we describe 27 cases in whom the onset of the symptoms of OMD was anatomically and temporally related to a prior trauma to the face or mouth. To draw attention to this disabling disease, we characterised the clinical features of post-traumatic OMD and compared it with primary OMD.

Patients and methods

One hundred and sixty patients with OMD were identified from the database of 9083 patients evaluated at Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic over a period of 20 years from 1977 to 1996. Twenty seven patients were identified as having peripherally induced, post-traumatic OMD using the following inclusion criteria: (1) the onset of the dystonia was within a few days or months (up to 1 year) after the injury; (2) the trauma was well documented by the patients' history or a review of their medical and dental records; and (3) the onset of dystonia was anatomically related to the site of injury (facial and oral). The exclusion criteria were: (1) secondary dystonia such as drug induced (tardive) dystonia, brain injury, Wilson's disease, and other recognised aetiologies of dystonia; (2) latency between the trauma and the onset of OMD was longer than 1 year; and (3) a strong psychogenic component.[13] The degree of the peripheral trauma was categorised as follows: 1=mild injury causing discomfort but without obvious abrasion or bleeding; 2=minor trauma or surgery with abrasion or bleeding; 3=moderate trauma requiring<1 week of medical care; and 4=major or multiple trauma or surgery requiring >1 week of medical care. The severity of the patient's symptoms was categorised as follows: 0=normal; 1=slight disability without functional impairment; 2=moderate

disability without functional impairment; 3=moderate disability with functional impairment (speaking/chewing/swallowing); and 4=incapacitated because of their inability to speak, chew, or swallow.

This group of patients with post-traumatic OMD was compared with a control group of 21 patients with primary (idiopathic) OMD randomly selected from our database of patients with primary (idiopathic) dystonia. Both groups of patients were compared for the following clinical variables: age at onset, duration of illness, type of movement disorder at onset, spread of symptoms and anatomical distribution, any potential predisposing factors, and response to various medications, including the number of medications, and response to botulinum toxin A (BTX-A) therapy. The response to various medications and to BTX-A therapy was assessed using a previously described clinical rating scale.[17] The "peak effect" score, defined as the maximum benefit after the injection, was rated on a 0–4 scale based on the information provided by the patients, daily diary of their symptoms, and interview of the spouse or friends (0=no effect; 1=mild improvement; 2=moderate improvement; 3=moderate improvement in severity and function; and 4=marked improvement in severity and function). In the post-traumatic group the following variables were also analysed: injury and disability rating, the correlation between the severity of the injury and severity of the OMD, and latency between trauma and the first appearance of OMD. The additional information was obtained by a questionnaire and a structured personal or telephone interview of the patients and their family members.

STATISTICAL ANALYSIS

The results of the response to medical and BTX-A therapy in both post-traumatic and primary groups were compared for significance using the two tailed Fisher's exact test. We compared both forms of the treatments for functional improvement scores (3–4) and no functional improvement (scores 0–2). Fisher's exact test was also used to determine the significance of the differences in the various clinical parameters seen in these two groups. The computer software used comprised SAS computer software by SAS Institute Inc, Cary, NC, USA, and Astute DDU Software, University of Leeds, Leeds, UK.

ILLUSTRATIVE CASES

Patient 1

This 61 year old woman underwent a series of dental procedures such as gingivectomy and braces for six months in 1979. Afterwards, she had cosmetic filling of her maxillary teeth followed by placement of three separate bridges. On the same day of this last procedure she noticed abnormal jaw movements which caused displacement of the left bridge. Since that time she has been unable to wear her lower dentures. Her mouth and jaw movements worsened gradually over the next 16 years. The patient also had mouth soreness on wearing her dentures and had difficulty in speaking clearly due to the painful spasms. Four years before our evaluation, her movements occurred only while wearing dentures and completely resolved within 30 minutes of their removal. The movements could be relieved by sensory tricks such as touching her tongue to the top of her mouth, biting her lips and, swallowing. The patient has been seen during the past 16 years by various dentists and physicians, without any medications being prescribed or a working diagnosis made.

Examination disclosed repetitive deviation of the mandible to the left, particularly when speaking and chewing. She had bilateral masseter spasms and considerable difficulty in moving her jaw to the right, particularly when the upper dentures were in place. She was injected with 195 units of BTX-A over two sessions and experienced dramatic relief of her symptoms (grade 4 improvement) for about 4 months during which she was able to wear her dentures without any discomfort.

Patient 2

This 42 year old woman had dentures fitted and correction of her overbite. She started adjusting her bite to get used to her new dentures. Three days after she started to use the dentures she noted difficulty in closing her mouth and experienced involuntary protrusion of her tongue. This worsened when she attempted to eat and she was able to tolerate only pureed diet. She stopped wearing her lower dentures due to involuntary tongue protrusion and her inability to close her mouth. She used sensory tricks such as pulling her face up with a finger, which enabled her to eat, but still had difficulty in swallowing. She developed right temporomandibular joint pain and popping of the joint. She was treated with trihexyphenidyl, which helped her spasms but she continued to have difficulty in eating. Examination in the resting position disclosed that she had 6–7 Hz frequency jaw tremors with lip pursing movements. Her jaw was deviated to the right. On opening her mouth she had rhythmical movements of her tongue and she had considerable difficulty in closing her jaw. An attempt to eat resulted in protrusion of her tongue, which kept pushing her food out and she was unable to close her mouth because of drawing of her chin and lower jaw downward and backwards. She had considerable difficulty in swallowing. In addition to OMD, she also had associated involuntary contraction of the corrugator, frontalis, and orbicularis oculi muscles with blepharospasm while eating.

Injections of BTX-A into the submental muscles on two occasions (25, 50 units) provided a grade 3 improvement. She is now able to eat, but still has difficulty closing her mouth when she drinks.

Results

Twenty seven patients (18 women) fulfilled the inclusion criteria for post-traumatic dystonia (table 1). The average age at onset of dystonia was 50.11 (SD 14.15) (range 16–73) years with a peak between 50 to 60 years of age. The

Table 1 Clinical features of patients with peripherally induced OMD

No	Age at onset/ sex	Type of injury	IR	DR	Latency (days)	Dystonia at onset	Dystonia at present	Possible predisposing factors
1	73/F	Ill fitting dental bridge	1	2	7	SD	SD, OMD, cranial	Essential tremor for 20 y, h/o WC, family history of tremor and TS
2	44/F	Gingivectomy followed by braces	3	3	1	OMD	OMD	None
3	42/F	Splint in TMJ	1	4	7	OMD	OMD, CD	
4	56/F	Multiple dental procedures, new dentures	2	3	14	OMD	CD, OMD	Edentulous state for 5 y
5	37/F	Facial trauma	2	3	56	Cranial, OMD, CD	Cranial, OMD, CD	
6	42/F	Root canal treatment	2	3	7	CD, OMD	CD, OMD	Previous CD, h/o haloperidol exposure to treat her CD
7	39/F	Extraction of the lower molar with institution of plates	3	3	112	OMD	OMD	
8	70/F	Surgery on left gum	3	2	5	OMD	OMD	H/o nerve pill 20 years ago
9	58/F	Oral surgery	3	4	10	Lingual	Cranial, OMD, CD	Bell's palsy 7 years ago, trigeminal neuralgia
10	62/M	Oral and facial trauma	4	3	180	OMD	OMD, CD	
11	37/F	Maxillary and mandibular osteotomy	4	4	120	OMD (unilateral jaw dystonia)	OMD	
12	53/F	Ill fitting dentures, dentures implant	1	3	14	OMD	OMD	
13	59/M	Root canal treatment, tooth extraction, apiocteny	2	4	7	OMD	OMD	
14	62/M	Frontal sinus obliteration	3	3	150	OMD	OMD	
15	39/F	New dentures with correction	1	4	3	OMD	OMD, cranial	
16	47/F	MVA with injury to chin and jaw, loss of teeth and broken dental plate	3	2	42	OMD	OMD, CD	
17	71/M	Gum infection with total dental extraction	3	4	1	OMD	OMD	
18	16/M	Gum surgery on upper and lower gum	3	2	4	OMD	OMD	Facial and abdominal tics
19	55/F	New braces	1	3	270	Lingual	OMD, CD, cranial	Face lift 9 years ago, rt hypoglossal palsy
20	60/F	Crowning of upper molar	1	3	14	Facial	OMD, CD, cranial	
21	60/F	Right TMJ arthroscopic surgery with breaking of adhesion. Joint manipulation, TMJ splint	3	4	3	OMD	OMD	Facial tics
22	68/M	Root canal treatment molar extraction, placement of upper partials	2	3	90	OMD	OMD	
23	24/M	MVA facial injury	4	3	365	SD, OMD	OMD, SD, CD, WC	Delayed milestones with stereotypies
24	50/M	Replacement of the cap	2	3	7	OMD	OMD, CD	Fx h/o of tremor
25	33/F	Facial and jaw injury	3	2	7	OMD	OMD	
26	56/F	New dentures which did not fit well	1	3	30	OMD	OMD	
27	40/M	Facial injury by football	1	3	224	OMD, CD, cranial	OMD, CD, cranial	ET

F=female; M=male; CD=cervical dystonia; SD=spasmodic dysphonia; WC=writer's cramp; ET=essential tremor; TS=Tourette's syndrome; IR=injury rating 0–4; DR=disability rating 0–4 (described earlier); MVA=motor vehicle accident; TMJ= temporomandibular joint; h/o=history of.

average duration of symptoms from onset to the patient's initial assessment at our clinic was 5.19 (SD) 3.86 (range 1–16) years. Four patients (5, 10, 23, and 27) had trauma involving their face or oral and dental structures. One patient (14) had frontal sinus obliteration. The remaining 22 patients had had at least one dental procedure before the onset of the OMD. The mean latency between the initial insult and the onset of the dystonia was 65 (SD 94) (range 1–365) days. Twelve patients had the onset of their symptoms within 1 week after trauma including two patients (2 and 17) who noticed the initial symptoms on the same day of the trauma. Most of our patients underwent extensive dental work before and after the onset of their symptoms with injury rating of 3 in 10 patients, and 4 in three (average 2 (SD 1). Four patients (4, 12, 15, and 26) had ill fitting dentures and one (1) had an ill fitting dental bridge. These patients gave a history of trying to adjust their bite by manipulating the jaw to adapt to the newly fitted dentures or the bridge. These manipulations and procedures were made before the onset of jaw spasms in all cases. There was no correlation between the injury grading and subsequent disability and severity of the dystonia (table 1).

All patients had symptoms predominantly involving the oromandibular region. The onset of symptoms was in the oromandibular region in 21 patients. One of these patients (11) had unilateral jaw spasms which progressed to OMD. Symptoms began as spasmodic dysphonia in two patients, in the tongue region in two, and in the face in one. One patient (6) had pre-existing cervical dystonia and the symptoms spread to the oromandibular region within 1 week after root canal treatment and 1 year after the onset of her cervical dystonia. The spread of the symptoms to cervical and cranial (facial and blepharospasm) region was noted in 52% of patients.

Of the 27 patients, 10 (37%) had possible predisposing factors which may have made them more prone to developing dystonia after injury. Two patients (1 and 27) had essential tremor, two (1 and 24) had a positive family history of essential tremor, and one had associated tics consistent with the diagnosis of

Table 2 Comparison of primary and post-traumatic OMD

Variables	*Primary*	*Post-traumatic*
Sex F/M	15/6	18/9
Duration of symptoms when first seen (y):		
Mean	3.62	5.19
SD	3.18	3.86
Range	1–12	1–16
Age at onset (y):		
Mean	51.48	50.11
SD	12.51	14.15
Range	23–74	16–73
Associated movement disorders (n (%)):		
Cervical dystonia	7 (33)	12 (44)
Blepharospasm	7 (33)	8 (30)
Writer's cramp	6 (29)	1 (4)*
Spasmodic dysphonia	8 (38)	2 (7)*
Essential tremor	3 (14)	2 (7)
Sensory tricks	7 (33)	9 (33)
Pain	6 (29)	14 (52)
Family history of MD	7 (33)	2 (7)*
Bruxism	7 (33)	4 (15)

*p<0.05. F=female; M=male; MD=movement disorder.

Tourette's syndrome. One patient was edentulous before placement of the dentures, but had no history suggestive of edentulous dyskinesia. She developed her symptoms 14 days after the placement of new dentures. One patient (6) had pre-existing cervical dystonia and had received haloperidol as a treatment for her cervical dystonia. Other conditions that may have predisposed these patients to peripherally induced OMD included possible exposure to neuroleptic drugs 10 years before the onset of dystonia, a history of tics, hypoglossal palsy, and a history of cosmetic facial surgery, Bell's palsy, trigeminal neuralgia, and delayed developmental milestones. As none of these possible predisposing factors have been validated, with the possible exception of family history of tremor, their relevance, if any, to the aetiology of dystonia in these patients is unknown.

Four patients (6, 9, 21, and 25) developed nocturnal bruxism after the onset of OMD with family history of bruxism in one (21). Three of these patients (21 and 25) also had diurnal bruxism. Five patients (3, 11, 15, 21, and 25) had associated temporomandibular joint symptoms; two (15 and 25) after the onset of their OMD. Three patients had temporomandibular joint symptoms before the onset of OMD. Two patients (3 and 21) had a temporomandibular joint syndrome, the treatment of which might have triggered the onset of OMD. One of these two had a temporomandibular joint splint and the other had temporomandibular joint arthroscopy before the onset of OMD. Three of the patients had extensive oral and temporomandibular joint surgery with worsening of their OMD after each intervention.

We compared this group of patients with post-traumatic OMD with 21 randomly selected patients (15 women) with primary OMD from our database as a control group. Their mean age at onset was 51.48 (SD 2.51) (range 23–74) years. The average duration of symptoms from the onset to our initial evaluation was 3.62 (SD 3.18) (range 1–12) years. Three patients had the onset of their dystonia in the cervical region, four had spasmodic dysphonia at onset, whereas two patients had their symptoms at onset in the cranial region. Seven patients had bruxism and four patients had temporomandibular joint symptoms.

There was no difference in any of the clinical variables when the two groups of OMD were compared (table 2). Although associated pain was more frequent in the post-traumatic group than in the primary group, the difference did not reach significance. Both groups used sensory tricks to alleviate their dystonia to the same degree. The most common sensory trick used by patients in both groups was bending their neck forward, which enabled them to eat. Essential tremor was the most often associated movement disorder in primary OMD compared with post-traumatic OMD; however, this difference did not reach significance. A family history of movement disorders was notably less frequent in the post-traumatic group ($p<0.05$). The frequencies of spasmodic dysphonia ($p<0.05$) and writer's cramp ($p<0.05$) were less common in patients with post-traumatic OMD than in the primary OMD group. Associated bruxism was less frequent in post- traumatic than primary OMD, but this difference did not reach significance.

The phenomenology, including the presence of resting or action dystonia, was similar in both groups. The spread of the symptoms to a contiguous anatomical region seemed more rapid in the post-traumatic group than in the primary group, but these data were not available on all patients due to inability of the patients to recollect the details of the spread of the initial symptoms. The severity of the symptoms was more pronounced in post-traumatic than primary OMD; however, the comparison of the disability scores did not reach significance.

Both groups received medical treatment and BTX-A injections. The average number of medications used in the post-traumatic group was four per patient and in the primary group three per patient. In the post-traumatic group 12 patients received trihexyphenidyl, which was the most commonly used drug. Baclofen and clonazepam were the next most common, used in six and seven patients respectively. The patients with jaw opening OMD received BTX-A injections in the submentalis complex whereas patients with jaw closing dystonia were predominantly injected in the masseters. In 21 patients who received BTX-A, nine (43%) had no functional improvement (scores 0, 1, and 2) and 12 (57%) patients had functional improvement (scores 3 and 4). In the primary group, 19 patients received BTX-A therapy. Six (32%) of these had no functional improvement, but 13 (68%) reported meaningful functional improvement. We compared the results to medical treatment using the same criteria and Fisher's exact test. The results indicated BTX-A therapy to be superior to the various forms of the medical treatment ($p<0.005$) in both groups. Five patients in the post-traumatic group and 11 in the primary group had complications after their first injections such as jaw weakness, loss of smile, dysphagia, nasal regurgitation, and jaw tremor. These complications were not seen with dose adjustment and improved techniques in subsequent treatment sessions.

Table 3 Summary of studies of post-traumatic oromandibular dystonia

Author/year	Nature of the trauma	Patients (n)	Latency (days)	Possible predisposing factors
Sutcher *et al* 1971[20]	Ill fitting dentures	4	Not known	Loss of proprioception
Jankovic and Van der Linden 1985[5]	Facial trauma	1	12 Months	Developmental delay
Koller *et al* 1983[21]	Dental extraction	Not known	Not known	None
Thompson *et al* 1986[18]	Dental	1	Not known	None
Brin *et al* 1986[23]	Oral surgery	2	3 Days to a week	Not known
Present study	Orofacial trauma	27	65 Days	Family history of movement disorder, prior exposure to neuroleptics, associated dystonia, essential tremor.

Discussion

Oromandibular dystonia is a focal dystonia which causes involuntary mouth closure or opening, deviation of the jaw, facial grimacing, and tongue movements. It may be accompanied by involuntary closure of the eyes (blepharospasm), strained or breathy voice (spasmodic dysphonia), cervical dystonia, or other movement disorders. Often misdiagnosed as a "dental problem", "temporomandibular joint syndrome", "psychological disturbance", or "bruxism", OMD may cause considerable functional and psychosocial disability.[16] The dystonia may be present only while eating and can be relieved by sensory tricks such as touching the face, pinching the neck, and bending the neck forward. The symptoms of OMD can be worsened by emotional factors, which is one of the reasons for the delay in the diagnosis. The cause of OMD is usually unknown (primary or idiopathic), but it may be associated with neuroleptic exposure, CNS trauma, hypoxic brain damage, metabolic disorders, and ischaemic or demyelinating lesions in the upper brain stem.[16] Rarely, peripheral trauma can induce dystonia. Although the concept of peripherally induced dystonia was first met with some skepticism, the notion that local trauma can lead to dystonia of the involved body part, sometimes also referred to as the dystonia-causalgia syndrome, is now well accepted.[4–15] Peripherally induced dystonia, however, is often not recognised, particularly if the trauma is relatively trivial or the latency between trauma and the onset of dystonia is longer than a few days.

The clinical features of peripherally induced OMD in our series were similar to those of primary OMD, with a few exceptions. Severity of symptoms and progression of the disease were more prominent in the post-traumatic group. Frequency of associated movement disorders such as essential tremor, bruxism, writer's cramp, and spasmodic dysphonia was lower in the post-traumatic group than in the patients with primary OMD, but the difference was significant only for writer's cramp and spasmodic dysphonia (table 2). Post-traumatic OMD had a lesser tendency to spread to contiguous or non-contiguous segments when compared with primary OMD. Family history of movement disorders was also less frequent in the post-traumatic group (7%) than the primary group (33%) ($p<0.05$). These data, however, must be interpreted cautiously because of the few cases in each group. The use of sensory tricks to relieve the dystonia was seen in both groups. This is by contrast with the usual absence of sensory tricks in other post-traumatic dystonias, such as cervical dystonia.[19]

Peripherally induced OMD has received little attention in the neurologial and dental literature and its true prevalence is unknown. In 1971, Sutcher *et al*[20] described four patients who developed jaw opening OMD after obtaining ill fitting dentures. Their patients had worn these dentures from a minimum of 1 year to many years before noticing the abnormal mouth movements. In our series four patients had new sets of dentures, including one patient with an ill fitting dental bridge. The patients with ill fitting dentures had a history of manipulating their jaw position using their jaw muscles to get used to the new dentures. These malaligned dentures may have caused an impairment of proprioception of the oral cavity leading to subsequent development of dystonia or so-called "edentulous dyskinesia".[20 21] We included one patient with OMD after facial injury in our original series of patients with peripherally induced dystonia.[5] In a series of patients with unilateral jaw and hemimasticatory spasms, Thompson *et al*[22] described a 42 year old woman who developed unilateral jaw dystonia after a dental extraction similar to that of our patients. Brin *et al*[23] briefly reported a series of 23 patients with post-traumatic limb, axial, cervical, spasmodic dysphonia, and generalised dystonia and included two patients with OMD after oral surgery. Koller *et al*[6] in their review of post-traumatic movement disorders described patients developing OMD after tooth extraction, but did not provide any details about the latency between the dental work and subsequent development of dystonia (table 3).

Our study shows that OMD can occur after an injury, oro-mandibular surgery, or a dental procedure. Although the relation between such insults and the subsequent development of OMD may be purely coincidental, the temporal and anatomical association, however, argues in favour of a cause and effect relation. Fourteen of our patients, eight with cranial dystonia before trauma and six with spread to cranial structures beyond the oromandibular region, may possibly have had or were significantly predisposed to developing cranial dystonia and the trauma may have exacerbated or precipitated the onset. Various predisposing factors, such as an associated movement disorder, family history of tremors, edentulous state, exposure to neuroleptic drugs, and peripheral nerve injury may contribute to the development of this movement disorder under some circumstances or in certain vulnerable people (table 3).[5 20–23] Seven of our 27 (26%) patients had possible predisposing factors such as a family history of movement disorders, prior exposure to neuroleptic drugs, delayed

milestones, history of movement disorders such as cervical dystonia, essential tremor, and tics.[4 5 24–27] It is not known, however, whether these factors play an important, or any, part in the mechanism of peripherally induced OMD. Fletcher *et al*[27] suggested that peripheral injury could trigger the onset of dystonia in genetically predisposed persons with primary generalised dystonia and that dystonia worsened after each subsequent injury. We made a similar finding in one of our patients who had preexisting cervical dystonia and developed OMD after root canal treatment. Three other patients noted exacerbation of their OMD after repeat oral surgeries. No correlation between the severity of the trauma and subsequent development of dystonia was established in our study (table 1).

A causative relation between peripheral injury and subsequent dystonia has been difficult to establish experimentally and there is no animal model that adequately mimics the clinical syndrome. Some experimental studies, however, suggest that peripheral injury can lead to reorganisation at cortical, subcortical, and spinal cord level resulting in motor dysfunction. The relation between peripheral trauma, pain, dystonia, and the frequent association with reflex sympathetic dystrophy further supports the notion that pathways subserving pain and those involved in motor control are important for peripherally induced movement disorders.[5 6–12] Direct demonstration of a relation between pain and basal ganglia came from de Ceballos *et al*.[28] They showed that a thermal injury to one hind limb in rats resulted in a delayed onset withdrawal of the affected limb and this was associated with a marked reduction of met-enkephalin and leu-enkephalin concentration in the globus pallidum bilaterally and only met-enkephalin in the caudate and putamen. These changes were most pronounced contralateral to the injured limb. They considered that the peptide changes occurred in response to the injury and were responsible for the subsequent motor impairment. There are many other examples of cortical or subcortical reorganisation in response to altered peripheral sensory input.[29 30] Further evidence for cortical changes after peripheral injury is the finding that patients with amputated limbs show larger motor evoked potentials and recruit a larger percentage of the motor neuron pool after transcortical stimulation in muscles proximal and ipsilateral to the amputated limb compared with the contralateral limb.[31 32]

Oromandibular dystonia, whether primary or post-traumatic, can lead to secondary complications. Bruxism, often associated with markedly increased dental wear, was more common in primary OMD (33%) than in post-traumatic OMD (15%), and 19% of our patients had associated temporomandibular joint syndrome, irrespective of the aetiology of the OMD. Therefore, to prevent these and other complications, prompt and appropriate treatment of OMD is important. Our findings suggest that OMD (primary and post-traumatic) responds poorly to various medications commonly used to treat dystonia, such as trihexyphenidyl, baclofen, and clonazepam. Injections of BTX-A into the affected muscles, although usually effective, is sometimes complicated by dysphagia and jaw weakness. These complications were encountered in 19% of the patients with post-traumatic and in 52% of those with primary dystonia. The complication rate, however, can be minimised if the treating physician has a detailed knowledge of the anatomy of oromandibular muscles and is skilled and experienced in treating this form of dystonia.

Despite growing evidence supporting the relation between trauma and subsequent development of dystonia, the physiological and biochemical meachanisms of peripherally induced dystonia, including OMD, are not well understood. Our series broadens the range of peripherally induced movement disorders and draws attention to the often unrecognised post-traumatic OMD.

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HISTORICAL NOTES

Early days of the tuning fork

Neurologists have for many years used the tuning fork both as a crude test for hearing, by means of the classic tests of HA Rinne (1819–1868)[1–3] and Weber-Liel (1832–1891), and for vibration sense. In Pavia, Italy, G Cardano, astrologer, physician, and mathematician, in 1550 suggested that sound could be transmitted through the bony skull as well as through the air and a few years later, H Capivacci, a physician in Padua, used this phenomenon as a means of differentiating between middle ear and nerve deafness.[4] The technique was then used by a German physician G C Schelhammer in 1684 who used a simple table fork. But, the study of ear diseases was in its infancy and little progress was made for two centuries.

The tuning fork was invented in 1711 by a John Shore, trumpeter and lutanist to both Henry Purcell and George Frederick Handel in London. The tuning fork found a place as a musical instrument employed in the concert halls, churches, and chamber music ensembles throughout Europe. It started as a small steel instrument consisting of a stem with two stout flat prongs, which on being made to vibrate produced a musical note of constant pitch, thus serving as a standard for tuning musical instruments and in acoustic investigations. In 1799 Young observed[5]: "The fundamental note was found to be one sixth of a tone higher than the respective octave of a tuningfork marked C"

E F F Chladni, a physicist in Wittenberg in about 1800, first systematically studied the mode of vibration of the tuning fork with its ·odal points. Using sets of tuning forks, he ade a musical instrument that failed to ieve popularity. J H Scheibler in Germany 334 produced a set of 54 tuning forks with e of 220 Hz to 440 Hz, at 4 Hz intervals. 's, J Lissajous created a tuning fork with ance box, intended to represent the nal standard of the note with 435 per second, but this too was not ccepted.[4] K R Koenig, a Parisian vised a clever clockwork mech- produced a continuous vibration and sound in the tuning fork. Hermann von Helmholtz in 1863 also used sets of electromagnetically powered tuning forks to elicit the sensations of tone. Until the electronic valve, the tuning fork was the only instrument that produced sinusoidal vibrations of standard duration.

Huizing[6 7] has reviewed the early papers on tuning fork tests of deafness. He relates that in 1855 Rinne compared hearing by air and bone conduction, and used the tuning fork for the diagnosis of deafness. However, before Rinne, Polansky in 1842 gave a detailed but forgotten description of the test and of its application in deafness. Schmalz in 1849 had made similar observations. Curiously, Rinne's report was also lost until Lucae (1880), Emerson (1884), and Schwabach (1885) confirmed the value of his work, since when it has retained the name of Rinne but not of Polansky.

Vibration sense

The concept of proprioceptive function, developed by Landry, Bell, Bastian, Ferrier, and others in the 19th century, advanced at the turn of the 20th century, and was further advanced by Sherrington[8] and later Haldane[9]: "The receptor organs are those parts of the living organism which are specially sensitive to the changes going on around them. Some of them are affected by the changes going on inside the body in muscles and joints and in the organ of balance (proprioceptors), others by the changes taking place in the world outside (exteroceptors)."

Kühne showed the presence of proprioceptive receptors in muscles ("Kühne's spindles") in 1862–3.

In Gowers' textbook of 1888[10] we find tactile, thermal, and pain sensory tests but he omits the sense of vibration. It was not until the beginning of the 20th century that tuning forks were applied to bony prominences and muscles to elicit "vibration sense" which was recognised as a crude method of testing neural pathways similar to those used in proprioception. Vibration was but repeated touch.[11]

Continued on page 733

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options and the efficacy of this treatment is mostly satisfactory. However, it is not complete and then there are some stones in CBD which not smashed or crashed by ESWL.

Aim To analyze the CBD.stone residues that ESWL was not effective.

Methods Twenty nine patients with CBD stones (Male 17, Female 12, mean age 68.1 yrs, range 33-90 yrs) were treated initially with ESWL (Richard Wolf Piezolith 2500) under radio focusing via PTCD, PTGBD and ENBD route. For the CBD stone residues that ESWL failed to smashed completely, endoscopic lithotripsy (EL) by using basket catheter was carried out after endoscopic sphincterotomy (EST) or endoscopic papillary balloon dilatation (EPBD). The recovery of these CBD stone residues were analyzed using the infrared spectrophotometry.

Results #1. Twenty patients (69%) with 1.5 stones (mean) were treated successfully with only ESWL. The average of ESWL frequency was 5.7. #2. Eight patients (28%) with 3.3 stones (mean) were failed to smash with ESWL, and then EST or EPBD was added to remove the stone fragments. #3. In the case of Mirizzi's syndrome (3%), a part of stone remained in the cystic duct, then the surgical treatment was carried out. #4. These stone residues (n=4) were analyzed by the infrared spectrophotometry and the major component of these residues was bilirubin calcium and the minor components were fatty acid calcium and cholesterol.

Conclusion These results suggest that #1. ESWL is an effective treatment for the patients with CBD stones, and ESWL following endoscopic lithotripsy raise the clearance rate of CBD stones and #2. the solidity of stones is a key factor whether the additional lithotripsy is necessary or not.

● **G2185**

IMMEDIATE REDUCTION OF PANCREATIC SO PRESSURE AFTER ENDOSCOPIC INJECTION OF BOTULINUM TOXIN (BoTox): IMPLICATIONS FOR PREVENTION OF ERCP-INDUCED PANCREATITIS. PI Okolo III, S Hill, K. Wadwa, CA Magee, PJ Pasricha, AN Kalloo. The Johns Hopkins School of Medicine, Baltimore, MD.

BoTox is a potent presynaptic inhibitor of cholinergic neurotransmission and has been shown to inhibit smooth muscle contraction. Pancreatic sphincter dysfunction has been implicated in the pathogenesis of ERCP-induced pancreatitis. We hypothesize that intrasphincteric BoTox will decrease pancreatic sphincter of Oddi (SO) pressure with important implications **Methods:** The study was performed in 2 phases. In the first phase (phase 1) we assessed the immediate effects of Botox on pancreatic SO motility. The pancreatic SO was identified by pancreatography and motility tracings were obtained using a low compliance pneumohydraulic capillary infusion system before and *immediately* after BoTox injection. In *phase 2*, 8 dogs were randomized to either intrasphincteric injection of BoTox or saline using a standard sclerotherapy needle into both major and minor papillae. Next pancreatitis was induced as previously described by radiographic contrast injection into the pancreatic duct under constant pressure for 120 seconds while acinarization was demonstrated fluoroscopically. 72 hours later, pancreatectomies were performed and the pancreatic specimens were scored by a blinded veterinary pathologist according to the degree of inflammation. **Results:** Phase1: In the BoTox group, there was a marked reduction in basal SO pressure following BoTox injection (mean 15.66 ± 2.08 vs 1.66 ± 1.15 mmHg, p=0.046). This effect was immediate. Phase 2: Using a graded score, the BoTox group had less inflammation than the saline group (17.5 ± 13.70 vs. 23 ± 22.41). This difference was, however, not statistically significant using the Mann-Whitney-2-sample statistic (P = 0.66). **Conclusion:** BoTox has an immediate effect in significantly reducing pancreatic SO pressure. This may have important implications for conditions where SO spasm may play a role such as ERCP induced pancreatitis. This reduction in pancreatic SO pressure may be therapeutically useful in conditions such as pancreatic SO dysfunction and in facilitating pancreatic endotherapy.

G2186

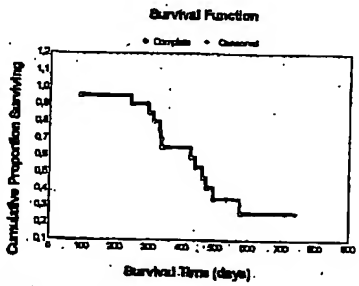
MICROENDOSCOPY. M. Ortner, M.Hünerbein*, J.Weber, J.Wirth, P.Schlag*, H.Lochs. IV Medical Dep. Charité, Surgical Dep. Robert-Rössle*, Humboldt-University, Berlin, Germany

Background: Visualization of small intrahepatic bile ducts and pancreatic stenosis by the perorally route can sometimes be difficult or impossible. **Aim:** To evaluate if new designed miniendoscops can overcome these problems. **Methods:** In seven patients cholangioscopy with standard instruments have failed to reach small intrahepatic bile ducts or could not bypass a stenosis in the bile duct or pancreatic duct. These patients were examined with miniendoscops of 0,6mm 3`000 pixel, 0,8 mm 6`000 pixel and Ø 1mm 10`000 pixel (ESA, Switzerland). Indications were evaluation of intrahepatic tumor spread in two patients with cholangiocarcinoma, suspected intrahepatic stones by ultrasonography not confirmed by ERCP in two patients, the dignity of a bile duct stenosis in one patient and suspect stenosis in chronic pancreatitis in two other patients. **Results:** These endoscopes can easily be introduced by means of 6 to 7 French catheters. They are also radio-opaque and so one can control the position by x-ray. The micro digital direct coupler camera-head with the 1/3 inchCCD-camera and the optic fiber bundle can be completely disinfected and sterilized (50°C). Different optics (45°,90° etc.) can easily be attached during the procedure. In our first experiences all regions of interest could be reached with these new miniendoscops and optically excellent pictures could be taken in the intrahepatic small bile ducts or in the stenosed areas, but the view in dilated common bile ducts is momentarily limited. For inspection of the ducts, endoprostheses do not have to be removed, because they can also easily be inserted beside them. At the moment an instrumentation channel is lacking. **Conclusion:** First experiences indicate that these miniendoscops could be of substantial value in special indications. Due to the low prices of these new miniendoscopes they could be additionally used in special indications. Further experience is necessary to assess their value in visualization of small ducts and otherwise un-passable stenosis. Mini endoscopes supplied freely by ESA.

● **G2187**

PHOTODYNAMIC THERAPY OF NON-RESECTABLE CHOLANGIOCELLULAR CARCINOMA. M.Ortner, J.Liebetruth*, A.Giesse, M.Hanft, J.Weber, J.Wirth, H.Lochs. 4th. Med Dep., Surgery Dep.* Charité University, Berlin, Germany

Background: Median survival time in advanced cholangiocellular carcinoma (CCC) is very poor with an average of 147 days. In a pilot study photodynamic therapy (PDT) showed good clinical result on jaundice and survival time (median 439 days). The **aim** of this study was to evaluate these preliminary results in a greater number of patients before initiating a randomized multicenter trial. Primary outcome parameter was reduction of cholestasis, secondary parameters were Quality of Life (Karnofsky index) and survival time. **Methods:** Twenty-one patients (age: median 59 (40 - 85), 10 female, 11 male;) with non-resectable CCC (Bismuth type: 17 IV, 3 IIIa, 1 II; Stage: 6 IV a, 14 IV b, 1 III) underwent PDT in addition to endoscopic drainage. The hematoporphyrin derivate Photofrin II (Quadra-Logica, Amsterdam, Holland) was infused intravenously (2 mg/kg bodyweight) and intraluminal photo-activation was performed by Argon dye laser two days later (wavelength 630 nm, 310 mW/cm², 180 J/cm², 400 µm fiber with 2,5 cm flexible cylindric diffuser tip). **Results:** Bilirubin decreased from 201.26 ± 189.25 µmol/l to 68.87 ± 78.27µmol/l ($p = 0.0051$) and Karnofsky-index improved from 49.04 ± 28.79% to 72.85 ± 19.01% ($p = 0.003$). Thirteen patients died (median survival time 336 days) and 8 patients are still alive (median survival time 504.5 days by an observation time of 292 to 739 days) (Table). **Conclusion:** PDT seems to be a useful therapeutic approach for non-resectable CCC. It is necessary to confirm these data in an extended randomized multicenter study.



Grant by the Charité University. Photofrin supplied by Quadra-Logica.

● **G2188**

THE VALUE OF PERORAL CHOLANGIOSCOPY. M. Ortner, D.Graebe, J.Weber, J.Wirth, H.Lochs. IV.Medical Dep. Charité, Humboldt-University, Berlin, Germany

Background: Cholangioscopy in the mother-baby technique is well accepted and widespread these days. **Aim:** In our study we wanted to evaluate how often the peroral approach is possible and if cholangioscopy brings more information than conventional ERCP. **Methods:** From 1995-1997 cholangiosocpy was performed in 89 patients in our department. Pentax and Fuji Babyscopes and percutaneous Olympus cholangioscops were used. The indication was diagnostic in 49 patients, therapeutic in 18 patients (12 photodynamic therapy in cholangiocarcinoma, 6 laser-lithotripsies), and tumor control after PDT in 22 patients. **Results:** In 83 patients (93.26%) the peroral route was possible and in 6 patients (6.74%) a percutaneous cholangioscopy had to be performed. In 82 of 83 patients (98.8%) the region of interest could be inspected by peroral cholangioscopy. Biopsies or cytology brushing through the peroral cholangiocops is still a problem. It was technically possible in only 12 patients (14.45%). In the other patients samples were obtained by fluoroscopic control (57 biopsies, 56 cytologies). Peroral diagnostic cholangioscopy (46 patients primary diagnostic and 21 patients restaging) brought confirmation of the ERCP diagnosis in 48 patients (71.4%), lead to change of the diagnosis in 4 patients (5.9%). In 21 patients the tumor extension was larger than seen by ERCP (31.34%). The suspected cholangioscopic diagnosis was wrong in 4 patients (5.9%). From the 16 therapeutic cholangioscopies all beside one laserlithotripsie could be performed successfully. Complication did not occur. **Conclusion:** Peroral cholangioscopy is a safe, technically easy procedure. The correct diagnosis can be established in most patients, although the biopsies techniques through the scope have to be improved.

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-----Original Message-----
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Strittmatter, M., Grauer, M., Isenberg, E., Hamann, G., Fischer, C., Hoffmann, K. H., Blaes, F., and Schimrigk, K. Cerebrospinal fluid neuropeptides and monoaminergic transmitters in patients with trigeminal neuralgia. **Headache 37(4): 211-6. 1997.**

Wehrmann, T., et al. Endoscopic botulinum toxin injectioninto the minor papilla for treatment for treatment for idiopathic recurrent pancreatitis in patients with pancreas divisum, **Gastrointestinal Endoscpoy, vol. 50, No. 4, 1999 pp. 545-548**, XP-000971257.

Okolo, P.I., et al., Immediate reduction of pancreatic so pressure after endoscopic injectionof botulinum toxin (BoTox): implications of prevention of ERCP-induced pancreatitis, **Gastroenterology, vol. 114, No. 4, Part 2, Apr. 1998, p. A535**, XP-000971724.

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Cerebrospinal Fluid N uropeptides and Monoaminergic Transmitters in Patients With Trigeminal Neuralgia

Matthias Strittmatter, MD; Markus Grauer; Elke Isenberg, MD; Gerhard Hamann, MD, PD; Christian Fischer; Karl-Heinz Hoffmann; Franz Blaes, MD; Klaus Schimrigk, MD

The pathogenesis of trigeminal neuralgia remains largely unknown. "Peripheral" as well as "central" causes have been suggested. To investigate the role of serotonergic, noradrenergic, dopaminergic, and peptidergic systems, we determined the concentrations of epinephrine, norepinephrine, and their breakdown product, vanillylmandelic acid, in the cerebrospinal fluid of 16 patients (55.3 ± 8.3 years) with trigeminal neuralgia. As a marker for the dopaminergic system, we determined cerebrospinal fluid concentrations of dopamine and its metabolite, homovanillic acid. As a marker for the serotonergic system, we measured cerebrospinal fluid levels of the serotonin metabolite, 5-hydroxyindoleacetic acid. In addition, levels of the neuropeptides, substance P and somatostatin, were determined.

The concentration of norepinephrine ($P<0.01$) and its metabolite, vanillylmandelic acid, ($P<0.05$) were significantly decreased in our patients. The level of the dopamine metabolite, homovanillic acid, was also significantly reduced ($P<0.01$). Also significantly decreased was 5-hydroxyindoleacetic acid ($P<0.01$). Substance P was significantly elevated ($P<0.05$). Somatostatin was significantly decreased ($P<0.05$).

We hypothesize that the sum of complex neurochemical changes plays a role in the pathogenesis of trigeminal neuralgia. The elevated substance P could support the concept of a neurogenic inflammation in the trigeminovascular system, whereas changes in the monoaminergic transmitters and their metabolites seem to reflect a more central dysfunction possibly due to a longer duration of the disease and an accompanying depression.

Key words: trigeminal neuralgia, CSF, transmitters, pain, neuropeptides, substance P

Abbreviations: VMA vanillylmandelic acid, 5-HIAA 5-hydroxyindoleacetic acid, HVA homovanillic acid, MPQ McGill Pain Questionnaire, PRI pain rating index, HPLC high pressure liquid chromatography

(*Headache* 1997;37:211-216)

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The pathogenesis of trigeminal neuralgia remains unknown. None of the numerous neuroanatomical,[1,2] neurosurgical,[3,4] and neuroradiological studies[5] explain the characteristics of the pain in trigeminal neuralgia, such as the sudden onset and the cessation of pain, the separation of the trigger zone from the area of pain, and the absence of sensory loss, even during the refractory period. Although many findings suggest a peripheral cause due to a chronic-intermittent irritation of the trigeminal nerve, some hypotheses involving central concepts such as reverberating circuits, ephaptic connections, and a disturbance of central synaptic activity have been postulated.[6,7]

Neurochemical studies point to a local inflammation of the trigeminovascular system in which the release of excitatory neuropeptides, such as substance P and somatostatin, plays an important role.[8,9] It is suspected that these mediators lead to plasma extravasation through an increase in the permeability of blood vessels. The changed interstitial environment and a stimulation of macrophages and mast cells result in an increased nociception and a perpetuation of the chronic inflammation. These local neurochemical processes are probably under central control. While there is little doubt that descending serotonergic and adrenergic systems modulate nociceptive transmission through the trigeminal system, it is not known whether these descending systems directly control neuropeptide release at the level of the primary afferent neuron.[10-12]

The goal of this study was to determine the concentrations of the neurotransmitters, epinephrine and norepinephrine, as well as their breakdown product, vanillylmandelic acid (VMA), in the cerebrospinal fluid (CSF) of 16 patients with trigeminal neuralgia. As a marker for the serotonergic system, we measured the breakdown product of se-

rotonin, 5-hydroxyindoleacetic acid (5-HIAA); as a marker for the dopaminergic system, we measured its breakdown product, homovanillic acid (HVA). In addition, the levels of the neuropeptides, substance P and somatostatin, were determined. These neurochemical parameters were correlated with each other and with the results of the McGill Pain Questionnaire (MPQ) to gain more insight into the pathophysiological mechanisms of trigeminal neuralgia.

PATIENTS AND METHODS

Patients.—Our study included 16 patients (mean age 53.3 ± 8.3 years, 11 men, 5 women) with trigeminal neuralgia. The average duration of disease was 5.2 ± 2.5 years, ranging from 2 to 10 years. Inclusion criteria were, according to the definition of the International Headache Classification, a paroxysmal, unilateral pain that can be triggered in the anatomical region of the trigeminal nerve, without any sensory or motor focal symptoms in this region.[13] Extensive tests including MRI and angiograms showed no cause for the trigeminal pain. All patients underwent conservative treatment until the onset of the study and received carbamazepine during the study in varying doses (600 to 1400 mg). None of the patients had received centrally active drugs such as antidepressants or neuroleptics.

The average frequency of attack during the study was 5.7 ± 2.2 per day. The subjective intensity of attacks was recorded with a standardized questionnaire (1=weak, 2=moderate, 3=severe); the average intensity was 2.3 ± 0.6 (Table 1).

To get a more differentiated picture of the pain, the patients were asked to fill out a German version of the MPQ.[14-16] The MPQ consists of a list of words (called items) that are arranged in groups and which describe pain sensation. The patient picks one word from each group. Each word has a defined point value attached to it and is classified as to whether it describes the sensory, affective, or evaluative qualities of pain. The number of words chosen per subcategory (affective, evaluative, and sensory) and the total point value, the so-called pain rating index (PRI), are computed. This gives an indication of the intensity and quality of the pain. For our patients, we calculated the PRI and the mean of the subgroups. Depressive symptoms were assessed by use of the Hamilton Depression Scale.[17] It consists of a questionnaire in which patients are asked how often (never, always, sometimes, etc) they harbor certain negative thoughts; eg, the feeling of isolation, suicide, etc. From the number of selected items and the frequency, a point value is computed which gives a semiquantitative measure for depression (Table 2).

Informed consent was obtained from all subjects, including controls. The study was carried out in accordance with the Helsinki Declaration.

Controls.—Fifteen age- and sex-matched controls, hospitalized with neurological diseases (mostly neuromuscular), were recruited (12 men, 3 women, average age 53.5 ± 4.3 years). Endocrine, metabolic, malignant, as well as acute or chronic inflammatory diseases were excluded through the history, clinical examination, and laboratory analysis.

Table 1.—Patient Characteristics

Patient	Sex	Age, y	Duration of Disease, y	Frequency of Attacks/d	Intensity of Attacks*
1	M	44	3	5	2
2	M	54	4	7	2
3	M	59	6	4	1
4	F	65	7	9	3
5	F	54	5	6	2
6	M	49	3	10	3
7	F	41	2	6	2
8	M	56	5	5	2
9	M	46	3	8	3
10	M	67	8	4	2
11	F	55	9	3	2
12	M	48	3	6	3
13	M	39	2	2	2
14	M	62	10	7	3
15	F	59	8	5	3
16	M	55	5	4	2

*Intensity: 1=slight, 2=moderate, 3=severe.

Table 2.—Results of the McGill Pain Questionnaire (MPQ)

Patient	MPQ, Pain Rating Index	MPQ, Affective	MPQ, Sensory	MPQ, Evaluative	MPQ, Miscellaneous	Hamilton Score
1	19	10	7	1	1	19
2	18	8	9	1	0	11
3	24	11	11	0	2	22
4	21	14	6	0	1	24
5	15	5	9	0	1	10
6	16	4	9	1	2	9
7	15	4	7	1	3	10
8	19	5	8	1	5	12
9	12	4	7	0	1	10
10	27	14	8	0	5	24
11	29	16	9	1	3	25
12	17	5	9	1	2	11
13	13	5	7	0	1	9
14	28	15	7	1	5	26
15	30	14	8	1	7	22
16	23	7	11	1	4	12

No control subject suffered from an acute or chronic pain syndrome.

Methods.—The lumbar puncture was always carried out at the same time in the morning (9 AM to 10 AM) after an overnight rest and fast. The first 9 mL of CSF were withdrawn without fractionating and immediately frozen on dry ice at -70°C for subsequent analysis.

To measure the concentration of catecholamines in CSF, a sample preparation kit (Recipe Chemicals and Instruments, No. 1020, Germany) was used. After a selective adsorption of the catecholamines onto activated aluminum oxide at pH 8.6, a desorption with perchloric acid was performed. For high pressure liquid chromatography (HPLC) separation, an RP 18e column was used (Merck, Darmstadt, Germany). The mobile phase consisted of 50 mM KH_2PO_4, 3 mM heptane sulfinic acid, 30 mg EDTA-Na_2, and 4.5% methanol with $HClO_4$ adjusted to pH 3.0. The flow rate was 1.2 mL/min. The electrochemical detection was carried out at a potential of 0.62 V and 50 nA/V with a 10 mV recorder input. The HPLC system was calibrated with plasma calibrators (Biorad, No. 195-5960, Munich, Germany). The computer-assessed calculation was done with the internal standard method. As an internal standard, dihydroxybenzylamine (DHBA) was used.

Details of storage, transport, and HPLC measurement of VMA, HVA, and 5-HIAA in the CSF were described earlier.[18]

The neuropeptides, somatostatin and substance P, were determined with a radioimmunoassay (DRG Instruments; DRP 7451, DRP 8001). Intra-assay and interassay variation coefficients were 5% and 12%. The detection limit of both assays was 8 fmol/mL. Duplicate measurements were taken.

Statistical Analysis.—All values are shown as mean ± standard deviation. To determine significance, *t*-test, ANOVA, and the Student-Newman-Keuls test were used. To correlate neurochemical and clinical parameters, we used the Spearman's rank correlation coefficient. To correct for the number of statistical tests performed, we used the Bonferroni inequality. Significances are indicated as $P<0.05$ or $P<0.01$.

RESULTS

The concentration of norepinephrine ($P<0.01$) and the concentrations of the catecholamine metabolites, HVA ($P<0.01$) and VMA ($P<0.05$), were significantly decreased in the CSF of patients suffering from trigeminal neuralgia compared to the control group.

Substance P was significantly elevated (45.4 ± 11.4 fmol/mL versus 34.2 ± 9.7 fmol/mL; $P<0.05$). Somatostatin was significantly decreased (36.2 ± 8.5 fmol/mL versus 25.3 ± 5.5 fmol/mL; $P<0.05$). 5-Hydroxyindoleacetic acid, the breakdown product of serotonin, was significantly decreased (86.8 ± 29.3 nmol/mL versus 159.1 ± 46.2 nmol/mL; $P<0.01$) (Table 3).

Epinephrine, 5-HIAA, and HVA in the CSF showed a significant negative correlation with the duration of the disease (Figure 1). The total PRI of the MPQ showed a significant negative correlation with epinephrine ($r=-.63$, $P<0.05$), HVA ($r=-.63$, $P<0.05$) and 5-HIAA ($r=-.65$, $P<0.05$) in the CSF. When differentiated into the subcategories of the MPQ, the affective score correlated significantly negatively with HVA ($r=-.67$, $P<0.05$) and 5-HIAA ($r=-.65$, $P<0.05$), whereas the sensory score correlated significantly with substance P ($r=.88$, $P<0.01$) and somatostatin ($r=.95$, $P<0.01$) (Table 4). There were no correlations of any of the neurochemical parameters in the CSF with age, sex, weight, or drug therapy.

Table 3.—Cerebrospinal Fluid Transmitters, Metabolites, and Neuropeptides in Patients With Trigeminal Neuralgia and Controls

	Trigeminal Neuralgia	Controls
Epinephrine, pmol/mL	368.6 ± 92.2	302.8 ± 75.1
Norepinephrine, pmol/mL	85.1 ± 33.1**	133.4 ± 52.1
Dopamine, pmol/mL	37.5 ± 19.8	39.5 ± 19.8
5-HIAA, nmol/mL	86.8 ± 29.3**	159.1 ± 46.2
HVA, nmol/mL	192.3 ± 46.0**	335.9 ± 72.2
VMA, nmol/mL	18.2 ± 6.5*	28.8 ± 15.7
SST, fmol/mL	25.3 ± 5.5*	36.2 ± 8.5
SP, fmol/mL	45.4 ± 11.4*	34.2 ± 9.7

*$P<0.05$, **$P<0.01$; calculation of significance by Student's *t*-test.
Values given as mean ± SD.
5-HIAA indicates 5-hydroxyindoleacetic acid, HVA homovanillic acid, VMA vanillylmandelic acid, SST somatostatin, SP substance P.

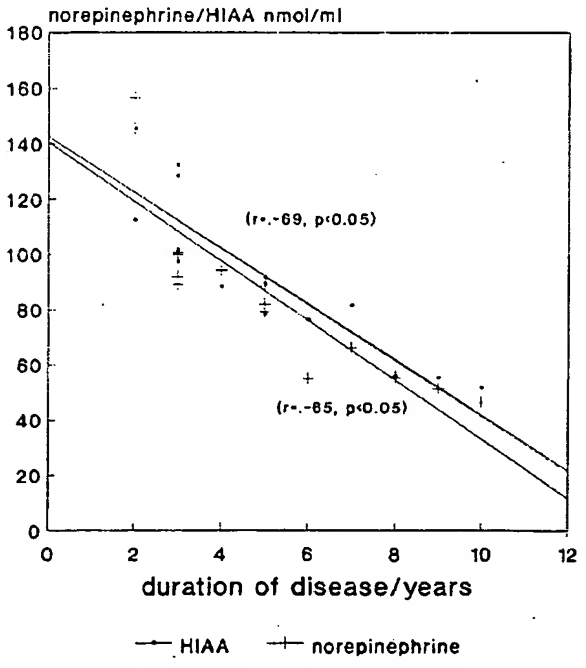

Fig 1.—Correlation between norepinephrine/5-HIAA and the duration of the disease.

Table 4.—Correlations Between Clinical Features and Neurochemical Parameters

	MPG, Pain Rating Index	MPG, Affective	MPQ, Sensory	Hamilton Score	Duration of Disease
Norepinephrine	-.57	-.50	-.39	-.44	-.50
Epinephrine	-.63*	-.39	-.18	-.38	-.65*
Dopamine	.14	-.05	.42	-.14	.15
HVA	-.63*	-.67*	-.15	-.70**	-.76**
5-HIAA	-.65*	-.65*	-.12	-.69**	-.77**
VMA	.11	.24	.22	.30	.19
SP	.16	-.07	.88**	-.17	.10
SST	.19	-.09	.95**	-.12	.03

*$P<0.05$.
**$P<0.01$.
Correlation coefficients by Pearson.
MPG indicates McGill Pain Questionnaire, HVA homovanillic acid, 5-HIAA 5-hydroxyindoleacetic acid, VMA vanillylmandelic acid, SP substance P, SST somatostatin.

Among the neurochemical parameters, substance P and somatostatin showed a significant negative correlation (r=-.72, $P<0.01$). Substance P also correlated with HVA (r=.77, $P<0.01$) and 5-HIAA (r=.68, $P<0.05$) (Figure 2). 5-Hydroxyindoleacetic acid and HVA correlated with each other (r=.61, $P<0.05$), and so did somatostatin and norepinephrine (r=.71, $P<0.01$).

COMMENTS

In the present study, substance P was significantly increased, whereas somatostatin and monoaminergic transmitters and their metabolites were found to be decreased in the CSF of patients with trigeminal neuralgia. So far, only a few studies have examined the concentrations of neurotransmitters in the ventricular compartments in patients with trigeminal neuralgia[19,20] which limits the comparability of the studies. Additional problems hindering the interpretation of our neurotransmitter data are the release and metabolism of these substances at the spinal level, their pulsatile release, and the dependence of these values on physical factors such as age, sex, weight, and height. However, with these limitations in mind, it is possible to draw some conclusions about pathochemical changes in trigeminal neuralgia.

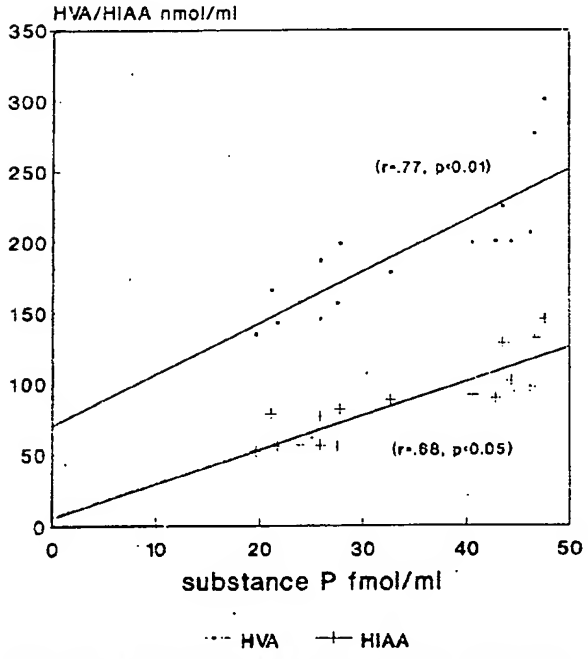

Fig 2.—Correlation between substance P and 5-HIAA/HVA.

In accordance with the only study published on this topic to date,[19,20] we found a significant increase of substance P in the CSF of patients with trigeminal neuralgia. Substance P plays an important role as a pain-inducing excitatory neurotransmitter in neurogenic inflammation,[21-24] and clinical studies have confirmed this role of substance P as an activator of afferent nociceptive structures in the anatomic region of the trigeminal nerve.[25] Together with the fact that recent studies stress the importance of the trigeminovascular system in trigeminal neuralgia,[8] this supports the hypothesis that continuing neurogenic inflammation is an important factor in the pathogenesis of this condition.

Unlike substance P, somatostatin was decreased in our patients. Somatostatin blocks the release of substance P from peripheral sensory nerve endings and has an antinociceptive effect.[26,27] Whether the deficiency of this generally inhibitory peptide is a necessary or sufficient condition for pain, and whether its effects

are mediated alone or in combination with other modulators, remains to be specifically tested.

The metabolite of serotonin, 5-HIAA, was significantly reduced. This is in accordance with other studies.[19,20] The antinociceptive effect of serotonin, mediated via descending, supraspinal pathways, together with dopamine and norepinephrine, has been known for some time.[10,28] Several studies have attempted to define high and low values of 5-HIAA in the CSF. Values between 50 and 90 ng/mL are considered low; values above 160 to 180 ng/mL are considered high.[29] According to these criteria, our patients with trigeminal neuralgia have low levels of 5-HIAA. Also, we observed in our patients that the lower the level of 5-HIAA, the higher the total score on the MPQ. We, therefore, hypothesize that reduced levels of serotonin are associated with depression and a lowering of the nociceptive threshold of these patients, leading to an exacerbation of the pain, independently of its etiology. Whether this is something that precedes the pain attacks or a result of these attacks, and whether this is typical for patients with trigeminal neuralgia, remains to be determined. Our finding of a correlation between substance P and 5-HIAA is confirmed by other studies showing that these substances comodulate a neurogenic inflammatory response in head and face pain.[30-33]

A metabolite of dopamine, HVA, was significantly reduced in our patients. Dopamine plays an important antinociceptive role in the central nervous system. Several studies have shown that the overall sensitivity towards pain is correlated with low levels of HVA and also with 5-HIAA.[34] Dopaminergic agonists such as pimozide reduce the pain in trigeminal neuralgia.[35] Again, it remains to be determined whether lower levels of HVA and dopamine precede or follow trigeminal neuralgia. Chronic pain syndromes are frequently accompanied by depressive symptoms and show decreased levels of HVA and 5-HIAA.[36,37] In our study, low levels of HVA and 5-HIAA also correlated with high scores on the affective subsection of the MPQ and high values on the Hamilton Depression scale which point to a major depressive component in trigeminal neuralgia. In addition, low levels of HVA and 5-HIAA correlated with the duration of the disease. Whether this is primarily the result of depression or dysregulation of descending inhibitory serotonergic and dopaminergic pathways in chronic pain syndromes is unclear.[37]

Substance P and monoamines are found together in the periaqueductal gray, reticular formation, descending spinal serotonergic pathways, the dorsal horn, and some limbic structures. Studies in cats have demonstrated the potential importance of high substance P levels because of its activation of the afferent nociceptive system of the head and its algesic effect in the trigeminal vascular system.[9] Our findings of elevated substance P and correlated dopamine, norepinephrine, and serotonin suggests that all these substances are codysfunctional and that for effective treatment each neuromodulator should be effected.[32]

In summary, our results point to complex neurochemical changes, which can be separated into local and more central changes, in the CSF of patients with trigeminal neuralgia. The increase in substance P, a major nociceptive neuromediator, supports the concept of a local neurogenic inflammation of the trigeminovascular system. Correlated with the duration of the disease and an accompanying depression, significantly lowered dopamine, norepinephrine, HVA, and 5-HIAA concentrations implicate a disturbance of central noradrenergic, dopaminergic, and serotonergic systems. In this way, a co-dysfunction of several neuromodulators, both monoamines and peptides, might be studied, and treatment algorithms designed.

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TI Peripherally induced oromandibular dystonia.
AU Sankhla, Charulata; Lai, Eugene C.; Jankovic, Joseph [Reprint author]
CS Movement Disord. Cin., Dep. Neurol., Baylor Coll. Med., 6550 Fannin, Suite 1801, Houston, TX 77030-3498, USA
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ANALYSIS OF AN EXCEPTIONAL MULTIPLEX FAMILY WITH GENERALIZED EPILEPSY I.E.Scheffer*, R.A.Howell, I.A.Oremek, G.J.Cliff and S.F.Berkovic, Department of Neurology, Austin Hospital, Heidelberg, Victoria.

The genetic basis of the generalized epilepsies is complex and poorly understood. Most family studies comprise small pedigrees with a few affected individuals. These studies have failed to elucidate the genetic relationships of the described syndromes of the generalized epilepsies, and their modes of inheritance. Large multiplex families with epilepsy are extremely rare, but provide an unique opportunity to clarify these issues as the abnormal genes must be relatively homogeneous.

We have studied a kindred with extensive genealogical data on 2000 members. In one branch of the family, with consanguinity in the higher generations, approximately half the individuals had generalized epilepsy. Of 31 affected family members in 4 generations, a variety of generalized seizure types beginning in childhood was seen. These included childhood generalized tonic-clonic seizures often with fever, absence attacks, myoclonic seizures, and rarely drop attacks; no cases had focal seizures. Affected family members could not be classified as having a single epilepsy syndrome. The pattern varied from a benign generalized epilepsy of early childhood, to a severe seizure disorder with refractory drop attacks persisting in adulthood with intellectual retardation.

The relative heterogeneity of generalized epileptic patterns in this family suggests that analysis of single electroclinical syndromes in disparate families may have less neurobiological relevance than the analysis of large multiplex families. The large number of affected individuals in this family is the result of consanguinity and provides a privileged opportunity to isolate specific epilepsy genes by molecular genetic studies.

EPILEPSY AND MOTOR VEHICLES: WHAT SHOULD BE THE GUIDELINES FOR DRIVING SAFETY? *JEC Constantinou, SS Gubbay. Department of Neurology, Princess Margaret Hospital for Children, Perth, W.A.

Thirty four of approximately 400 drivers with epilepsy (8.5%) followed prospectively over a period of eleven years sustained a seizure while driving. The application of a "one year rule" would have prevented the majority of driving incidents without unreasonably restricting the right to drive as the majority of drivers (71%) reported at least one seizure within one year of the driving incident. There were only three cases (9%) in which a seizure had occurred at an interval of between one and two years prior to the event. Five patients (15%) had been seizure free for more than two years. The most important factor in assessing the risk faced by the epileptic driver was seizure frequency. Eleven patients (32%) suffered from at least monthly seizures. Personal injury and property and vehicle damage (55% of incidents) were generally of minor degree, though there were two instances of serious personal injury. Six of the subjects (18%) citing unnecessary hardship, continued to drive despite involvement in multiple accidents. While realistic and humane guidelines encourage motivation to seizure control in most patients the intransigent driver provides particular ethical difficulties.

Automatisms - An analysis of the current legal position with reference to clinical practice and medicolegal interpretation.
Roy G Beran, The Liverpool Hospital

The social and psychological pressures that shape our criminals also shape those who make and remake the laws which control them. The interface between medicine and the law is an area which demands further investigation. There can be no criminal capability for an act unless the perpetrator had both the will to so act and the capacity to differentiate and choose whether or not to conform the particular behaviour to that dictated by the law. The capacity for choice must remain the fundamental issue. The range of conditions which can raise volition as a defence include: Somnambulism; post-traumatic syndromes; epilepsy; arteriosclerosis; or acts secondary to cerebral neoplasia. There is need to differentiate between "reflex actions" and "automatisms" and it is imperative that terms such as automatism or automatic behaviour are not perverted to allow an excuse for that which is inexcusable. Cases such as that of Cogdon, who was acquitted of murdering her daughter; Ramsbottom who was found guilty of causing a traffic accident despite having a stroke; Dennison in which a driver was found guilty despite epilepsy or; Jenkins where the driver was initially found innocent of dangerous driving because of the unpredictable nature of diabetes will be discussed. Special attention will be focused upon the case of Sullivan, a landmark in consideration of automatisms in epilepsy. The paper will examine "insane" verses "non-insane" automatism and the Australian legal system as it affects modern neurological practice. Suggestions will be proffered as to how the law should be modified to better reflect justice as required within the context of modern medical knowledge.

THE USE OF BOTULINUM TOXIN IN THE TREATMENT OF ORO-MANDIBULAR DYSTONIAS AND FRACTURES OF THE MANDIBULAR CONDYLE. G. McKellar and I. Lorentz* Westmead Hospital, Westmead, N.S.W. 2145, Australia.

We treated 9 patients with Meige syndrome, 7 with masticatory muscle dysfunction, 2 with bruxism. One to 6 injections of Botox were given usually under E.M.G. guidance. Ten to forty mouse units of Botox were given per muscle. Videos were taken before and after Rx. Assessment was made on subjective responses, but these were substantiated by objective measurements. 37 treatment courses were successful and 5 injections were failures. Dysphagia occurred in 2 patients only, and other side effects were insignificant. Four patients with fractures of the mandibular condyle were treated with Botox in order to reduce muscle spasm prior to surgical reduction of the fractures. The results were excellent in all 4 patients. Botox may have important applications in Dental surgery as well as in Neurology.